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12-15-03

21838

IN THE PATENT AND TRADEMARK OFFICE

Inventor	Tibor GIZUR et al
Patent App.	09/856,517 (US Nat'l phase of PCT/HU99/00102)
Filed	21 May 2001 Conf. No. 9138
For	PROCESS FOR THE SYNTHESIS OF 1-(AMINOMETHYL)CYCLOHEXYL-ACETIC ACID
Art Unit	1625 Examiner Oh, T

Hon. Commissioner of Patents
Box 1450
Alexandria, VA 22313-1450

Appealed 15-Oct-03

APPEAL BRIEF UNDER 37 CFR 1.192(a)

Now come appellants by their duly authorized attorney and submit their brief under the provisions of 37 CFR 1.192(a).

REAL PARTY IN INTEREST

The real party in interest is Richter Gedeon Vegyeszeti Gyar RT, Budapest, Hungary,

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences involving the instant application.

(3) STATUS OF CLAIMS

Claims 10 through 18 are in the application. Claim 10 has been finally rejected under 35 USC 112, first paragraph, as beyond the scope of the enabling disclosure provided by the

specification and under 35 USC 112, second paragraph, as indefinite. Claims 11 through 18 have been rejected solely because these claims are dependent upon rejected base claim 10. In fact, however, claims 14 through 17 are not dependent upon claim 10 and are directed to new intermediate compounds of the Formula (II) which are the starting materials used in the process of claims 10 through 13 and 18 to prepare pure 1-(aminomethyl)-cyclohexyl-acetic acid or a pharmaceutically acceptable salt thereof.

(4) STATUS OF AMENDMENTS

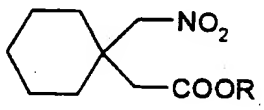
Appellants have filed an amendment on 18 April 2003 in which the present claims 10 through 18 were again presented for examination. On 15 July 2003 the Examiner finally rejected independent claim 10 under 35 USC 112, first paragraph, as beyond the scope of the enabling disclosure and under 35 USC 112, second paragraph as indefinite and rejected all of the remaining claims as dependent upon rejected base claim 10. The rejection of claim 10 under 35 USC 112, second paragraph, as indefinite was a new basis for rejection.

(5) SUMMARY OF INVENTION

Appellants have discovered an invention with two particular features. One feature is a process for the preparation of pure (1-aminomethyl)-cyclohexyl acetic acid or a pharmaceutically acceptable salt thereof. This compound is an established pharmaceutically active ingredient known as gabapentin and is useful to

antagonize gamma-amino-butyric acid (GABA). See the original application on page 4, lines 27 and 28 through page 5, line 21 that shows the synthesis of the compound of the Formula (I) from the new compound of the Formula (II). Thus the compound of the Formula (I) or a pharmaceutically acceptable salt thereof is prepared by:

(a) catalytically hydrogenating a compound of the Formula (II)



(II)

wherein

R is hydrogen, benzyl or diphenylmethyl or aryl which is unsubstituted or substituted by a C_1 to C_4 alkyl or alkoxy group in the presence of a hydrogenation catalyst in an inert organic solvent at a temperature of 10 to 50°C under 1 to 20 kPa pressure to directly obtain the 1-(aminomethyl)-cyclohexyl-acetic acid in the inert organic solvent;

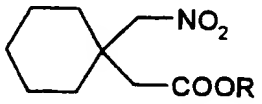
(b) filtering the 1-(aminomethyl)-cyclohexyl-acetic acid in the inert organic solvent prepared according to step (a) to remove the hydrogenation catalyst to obtain a filtrate;

c) concentrating the filtrate by removing a portion of the inert organic solvent to obtain pure 1-(aminomethyl)-cyclohexyl-acetic acid; and

(d) in the case where a pharmaceutically acceptable salt is to be formed transforming the pure 1-(aminomethyl)-cyclohexyl-acetic acid into a pharmaceutically acceptable salt.

See also Example 1, part (b), appearing in the original application on page 6, lines 5 through 11 and Example 2 appearing in the original application on page 6, lines 13 through 21.

The second feature of the invention relates to the new structurally distinct compounds of the Formula (II)



(II)

wherein R is hydrogen, benzyl or diphenylmethyl or an aryl group which is unsubstituted or substituted by a C1 to C4 alkyl or alkoxy group. These new compounds of the Formula (II) are the starting materials in the present process used to prepare the desired pure (1-aminomethyl)-cyclohexyl acetic acid or a pharmaceutically acceptable salt thereof.

Appellants have found that where a new compound of the Formula (II) where R is hydrogen or R is benzyl, diphenylmethyl or aryl unsubstituted or substituted by alkyl or alkoxy, is hydrogenated in an inert organic solvent at a temperature of 10 to

50°C under 1 to 20 kPa pressure to directly obtain the desired 1-(aminomethyl)-cyclohexyl-acetic acid in an inert organic solvent, the product is obtained in high purity without formation of the spirolactam as shown in col. 5, line 40 of U.S. Patent 5,091,567 to GEIBEL et al. See page 4, lines 12 to 17 of the present application.

According to GEIBEL et al in col. 5, lines 30 to 40 when the starting compound in step 5) of the reference process is the ethyl ester instead of the free acid, or the benzyl, diphenylmethyl or aryl ester of the present Formula (II) the principal product obtained is the spirolactam which must then be treated with an acidic ion exchanger to eventually obtain the desired 1-(aminomethyl)-cyclohexyl-acetic acid. Only a small amount of the 1-(aminomethyl)-cyclohexyl-acetic acid is obtained by direct hydrogenation of the ethyl ester according to GEIBEL et al.

Both the new compound of the present Formula (II) where R is hydrogen (Formula IIa) or the new compound of the Formula (II) where R is benzyl, diphenylmethyl or aryl (Formula IIb) are key to successfully carrying out step (a) of claim 10 to obtain the desired 1-(aminomethyl)-cyclohexyl-acetic acid without the lactam formation. See page 1, lines 3 through 10 of the original application and original claims 6 through 9.

(6) THE ISSUES

The first issue is the scope of the hydrogenation catalyst in claim 10, step (a) which is directed to catalytically hydrogenating a compound of the Formula (II) in the presence of a

hydrogenation catalyst in an inert organic solvent at a temperature of 10 to 50°C under 1 to 20 kPa pressure to directly obtain the 1-(aminomethyl)-cyclohexyl-acetic acid in the inert organic solvent. The Examiner believes that the scope of the hydrogenation catalyst in claim 10 has not been enabled according to the requirements of 35 USC 112, first paragraph.

The second issue is whether Appellants' definition of the solvent used in the catalytic hydrogenation according to claim 10, step (a), as "an inert organic solvent" is indefinite for failure to particularly point out and distinctly claim the subject matter of the invention according to the requirements of 35 USC 112, second paragraph.

(7) GROUPING OF CLAIMS

Claim 10 is the only claim in the case that has been rejected under 35 USC 112, first paragraph, as beyond the scope of the enabling disclosure. Claim 10 is directed to a process for preparing a compound of the Formula (I) or a pharmaceutically acceptable salt thereof and the first step of the process involves the catalytic hydrogenation of the starting material of the Formula (II) with a hydrogenation catalyst. The Examiner has rejected claim 10 under 35 USC 112, first paragraph, on the grounds that the broad definition of the hydrogenation catalyst in step (a) is beyond the scope of the enabling disclosure. Claims 12 and 18 are dependent upon rejected base claim 10 and have been rejected solely because of the rejection of claim 10. Claims 12 and 18 have a more

limited definition of the hydrogenation catalyst than does claim 10, the Examiner has not specifically questioned the enablement of the hydrogenation catalysts defined in claim 12 and 18, and for this reason claims 12 and 18 do not stand or fall together with claim 10 on this issue. In fact the Examiner has indicated in Paper Number 11 at the top of page 3 that claims 11 through 18 have been rejected as being dependent on a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 13 is dependent upon claim 10 and limits the "inert organic solvent" called for in step (a) to a C1 to C4 alcohol. The Examiner has rejected claim 10 under 35 USC 112, second paragraph, as indefinite, on the grounds that "inert organic solvent" fails to particularly point out and distinctly claim what Appellants regard as their invention. The Examiner has not rejected claim 13 on this basis, however, since claim 13 limits the "inert organic solvent" to a C1 to C4 alcohol. Thus claim 13 does not stand or fall together with claim 10 on this issue.

Claims 14 through 17 are directed to new structurally distinct compounds of the Formula (II) which are the starting materials in the process of claim 10 for the preparation of the compound of the Formula (I) or a pharmaceutically acceptable salt thereof. Claims 14 through 17 are entirely independent of claim 10, are directed to a feature of the invention that is separate and distinct from the pure compound of the Formula (I) or pharmaceutically acceptable salt obtained according to the process of claim 10

and no basis for rejection of these claims has been set forth heretofore by the Examiner. It is noted that the scope of the definition of the hydrogenation catalyst in step (a) of claim 10 and the question of whether the term "inert organic solvent" is vague and indefinite have absolutely nothing to do with claims 14 through 17 directed to the new structurally distinct compounds of the Formula (II) where R is hydrogen, benzyl, diphenylmethyl or aryl unsubstituted or substituted by a C1 to C4 alkyl or alkoxy group.

For the reasons stated above, claim 10 does not stand or fall together with claims 12 and 13 through 18.

(8) THE ARGUMENTS

37 CFR 1.192 (c)(8)(i)(B)

The Examiner is Incorrect for Rejecting Claim 10 under 35 USC 112, first Paragraph, on the Grounds that the Claim is Supported by a Non-Enabling Disclosure

The Examiner has rejected the independent process of preparation claim 10 under 35 USC 112, first paragraph, on the grounds that the claim is not supported by an enabling disclosure. Specifically the Examiner is troubled by the broad term in line 10 "hydrogenation catalyst" which the Examiner considers to be too broad since the only hydrogenation catalyst that Appellants have successfully exemplified in the specification to hydrogenate a compound of the Formula (II) to form a compound of the Formula (III) is palladium on activated carbon. The Examiner is aware that

Appellants name other hydrogenation catalysts on page 4, lines 22 through 26 of the original specification. There Appellants mention "rare metal catalysts, e.g. rhodium or palladium, Raney nickel or cobalt catalysts.." The Examiner argues, however, that catalysis is an unpredictable art and the only hydrogenation catalyst that Applicants have shown to successfully hydrogenate a compound of the Formula (II) is palladium-on-carbon.

Appellants do not agree that catalytic hydrogenation is so unpredictable. Catalytic hydrogenation of nitro compounds to obtain amino compounds has been known to those "skilled in the art" for many years and such a hydrogenation step is a common process used in organic synthesis. In such a process several types of hydrogenation catalysts can be used interchangeably so that one hydrogenation catalyst can be routinely substituted for another to obtain the same product with perhaps only some difference in product yield or purity. Therefore in principle it is highly predictable that the well-known and commonly used catalysts may be substituted for one another in hydrogenation of a nitro compound to form the corresponding amino compound. One "skilled in the art" knowing that the use of Raney nickel to catalyze the hydrogenation of a nitro compound to form the amino compound would also work if palladium were substituted as hydrogenation catalyst for the Raney nickel.

Appellants note that claim 1 of U.S. Patent 5,091,567 to GEIBEL et al defines the hydrogenation catalyst as "a noble metal catalyst" even though the only noble catalyst that is exemplified

(see Examples 8 and 15) or even named (see col. 5, lines 46 and 47) in the reference is palladium-on-carbon.

The Examiner has made an argument that case law written by the U.S. Patent and Trademark Office Board of Appeals and by the Courts supports the Examiner's argument that the definition of the hydrogenation catalyst should be limited because catalysis is an unpredictable art and more than routine experimentation would be needed to determine which hydrogenation catalysts known in the art would actually work to reduce the present Formula (II) compound to form the Formula (I) compound and which would not work. The Examiner has cited In re Wands, 8 USPQ 2d 1400 (CAFC 1988) and Ex parte Forman, et al, 230 USPQ 546 (PTO Bd. App. 1986) when he mentions "Forman factors or Wands factors" on page 2 of Paper No. 7. Appellants do not believe that either of these decisions is relevant to the present case. In Forman the Examiner did raise the issues of enablement and undue experimentation under 35 USC 112, first paragraph, just as in the present case, but the facts are so far removed from the present case, that the decision is not applicable. The Forman decision does not relate to catalytic hydrogenation, but relates to a new vaccine for immunizing a patient against enteric diseases. with a genetic hybrid bacterium as the active ingredient. In Forman the questions of enablement and undue experimentation relate to how the active ingredient in the vaccine is prepared. The Examiner argued that one of the starting materials, a particular S. typhi mutant strain was not commercially available and in the absence of a permanent deposit by th appli-

cant, one "skilled in the art" could not make the active ingredient for the vaccine without the need to carry out undue experimentation. The Examiner also argued that the process used to prepare the active ingredient in Forman, known as hyperconjugation, is a new process and it is unpredictable as to the results that will be obtained. The fact that the Patent and Trademark Office Board of Appeals agreed with the examiner in Forman that the application did not contain a sufficient disclosure to enable the practice of the invention in no way provides any basis for the Examiner's rejection of the claims in the present application for lack of enablement. While there may be some unpredictability associated with catalysis, catalytic hydrogenation is an old, well-known process unlike hyperconjugation and so Forman should not apply. The broad definition of the hydrogenation catalyst as a noble metal found in the independent claim of U.S. Patent 5,091,567 supports Appellants' argument that catalytic hydrogenation is not the equivalent of hyperconjugation in terms of predictability.

The Wands decision is also a decision in the biotech field that does not relate to catalytic hydrogenation. The Wands decision relates to an immunoassay method for the hepatitis B surface antigen (HbsAg) using high affinity monoclonal antibodies of the IgM isotype and that these particular monoclonal antibodies detected the antigen with surprisingly high sensitivity and specificity. The Examiner argued that the specification in Wands was not enabling because (1) there was no deposit in a permanent depository of the hybridomas needed to secrete the monoclonal

antibodies and (2) there was not enough disclosure of how to produce the high affinity monoclonal antibodies of the IgM isotype without the need to conduct undue experimentation since the data in the Wands application showed that the process to produce such monoclonal antibodies was unpredictable and unreliable and would require undue experimentation of one "skilled in the art" trying to practice the Wands invention. Specifically only a fraction of the hybridomas produced by Wands in the fusion process produced monoclonal antibodies that were effective in binding to the HbsAg. Thus the examiner and the Board of Appeals considered the Wands process to be too unpredictable and required an undue amount of experimentation to successfully practice the invention. Furthermore the examiner and the Board of Appeals concluded that in the absence of a deposit of the viable hybridomas in a permanent depository, the enablement requirement of the patent statute was not satisfied.

The Court ruled that none of the arguments by the Examiner or the Board was sustainable and reversed the rejection of the claims as based upon an inadequate disclosure. The Court made it clear that there is no requirement of depositing the hybridomas in a permanent depository when the specification itself would enable one "skilled in the art" to prepare without the need to conduct undue experimentation hybridomas that will secrete the monoclonal antibodies. Furthermore the fact that one would have to screen hybridomas to find out which ones produce viable monoclonals does not amount to "undue experimentation" even if the majority of

the hybridomas do not produce the viable monoclonals. Such experimentation would be expected. Thus the Court ruled in favor of the applicant and against the Patent and Trademark Office. Thus the Wands decision in no way supports the Examiner's argument that the present application is not enabling to support the catalytic hydrogenation as presently claimed.

In fact Wands is actually supportive of the Applicants' position since Wands makes it clear that a certain amount of experimentation is entirely acceptable in practicing the invention disclosed in a U.S. Patent. In the present case one "skilled in the art" could pick and choose among conventional hydrogenation catalysts such as a platinum group metal or Raney nickel and determine which ones catalyze the hydrogenation of the Formula (II) compound the best.

The Examiner has also cited Ex parte Sizto, 9 USPQ 2d 2081 (Bd. App. 1988) to provide support for his argument that catalysis is an unpredictable art. In Sizto an analytical method is claimed using a catalyst which facilitates a reaction between an analyte (unknown) and a solute (reagent). Such a reaction permits the determination of the presence or absence of the analyte in a given sample. The process claims a "catalyst" without any further qualification whatsoever even though the only catalyst actually exemplified in but one example is an enzyme. The examiner and the Board of Appeals both agreed that the term catalyst was too broad because there was no limitation whatsoever on the identity or the function of the catalyst. The Board specifically pointed out that

there are many catalysts that are not enzymes and there is no evidence that any catalyst that is not an enzyme will work in the Sizto method. Other catalysts that were originally contemplated by Sizto included metal complexes and electron transfer agents which are far removed from enzymes. Furthermore the Board noted that one of the other reagents in the analytical method had to be an enzyme even where the applicant planned to use a non-enzyme catalyst. The Board indicated that it was highly speculative that such a method would work where the catalyst was anything but an enzyme and affirmed the rejection.

The present process is directed to the catalytic hydrogenation of a nitro compound of the Formula (II) using a hydrogenation catalyst. Hydrogenation catalysts are typically metals and do not encompass enzymes or the other diverse kinds of catalysts mentioned in Sizto. The holding in Sizto is not that catalysis in general is unpredictable, but that the kind of catalysis called for by the analytical method of Sizto is unpredictable if catalysts other than enzymes are contemplated. Thus Sizto provides no basis for the Examiner's requirement that Appellants limit the catalyst in their hydrogenation process to palladium-on-carbon.

The Examiner has also cited In re Armbruster, 185 USPQ 152 (CCPA 1975) which is directed to a process for hydrolyzing starch to obtain a starch product having a dextrose equivalent (D.E.) less than 15 using bacterial alpha-amylase to increase the D.E. The application also disclosed that the process was useful to obtain a starch hydrolysate with a D.E. of 5 to 15. The examiner

took the range of 5 to 15 to mean that a starch hydrolysate with a D.E. less than 5 would not be operative. The issue here was not the scope of the kinds of enzymes used to facilitate the hydrolysis, but whether the applicant really established that his process could obtain the starch hydrolysate product having a D.E. less than 15, including a D.E. below 5 is still a useful product. The Court held that the examiner had insufficient evidence to establish that a starch hydrolysate with a D.E. less than 5 would be inoperative and only made such a speculation based upon the lower end of this disclosed range.

There is no similarity whatsoever between the facts in Armbruster and those in the present case since the process in the present case includes no range where one portion of that range arguably could encompass inoperative subject matter. Furthermore the Court in Armbruster ruled in favor of the appellant and against the Patent and Trademark Office on the issue of enablement and so the decision actually helps the present Appellants more than it helps the Examiner's position. Nothing in the Armbruster decision supports any argument that the claims in the present case with the broadly defined hydrogenation catalyst cover catalysts that will not work and the decision leaves it to the Examiner to prove that any such catalyst within the scope of the presently claimed invention will not work.

Finally In re Angstadt and Griffin, 190 USPQ 1976 (CCPA 1976) has been cited for its disclosure that catalytic processes are unpredictable and that the scope of the enablement varies

inversely with the degree of unpredictability. The examiner and the Board of Appeals questioned whether the claimed process which was a process to catalytically oxidize secondary or tertiary alkyl aromatic hydrocarbons to form a reaction mixture containing the corresponding hydroperoxide using an organometallic complex as the catalyst. The application also stated that some of the catalyst complexes will not effectively facilitate oxidation of the starting materials. The Court reversed the examiner and the Board stating that the evidence as a whole showed that the process was operative notwithstanding that some particular catalysts may be inoperative. The Court held essentially that some experimentation by one "skilled in the art" seeking to work the patent to find the best catalysts for the process does not amount to "undue experimentation" and is permissible under the patent statute. Thus this decision is supportive of the right of the present Appellants to obtain a patent with the broad definition of the hydrogenation catalyst.

Furthermore Appellants have carried out additional examples showing catalytic hydrogenation of the compound of the Formula (II) where R is hydrogen to yield 1-(aminomethyl)cyclohexyl acetic acid of the Formula (I). Instead of palladium, the catalysts tested were Raney nickel and Adams catalyst. The examples are as follows:

Example 3

1-(nitromethyl)cyclohexane acetic acid (6.27 g; 0.031 mol) was dissolved in methanol (75 ml). To the solution Raney Ni catalyst (1 g) was added and was hydrogenated at atmospheric

pressure. The catalyst was filtered off and the filtrate was evaporated in vacuo. To a residue was added tetrahydrofuran (60 ml). The crystalline product was filtered off and dried.

Yield: 2.1 g (39.6 %)

Melting point: 165-9°C

Example 4

1-(nitromethyl)cyclohexane acetic acid (6.27 g; 0.031 mol) was dissolved in methanol (75 ml). To a solution Adams catalyst (0.07 g) was added and was hydrogenated at atmospheric pressure. The catalyst was filtered off and the filtrate was evaporated in vacuo. To the residue was added tetrahydrofuran (60 ml). The crystalline product was filtered off and dried.

The examples show clearly that the hydrogenation process can be carried out with other types of catalysts.

Appellants have made these additional examples of record on 16 May 2003 in a Declaration Under 37 CFR 1.132 signed by Dr. Tibor Gizur, one of the Appellants. In the declaration, Dr. Gizur concluded as follows:

that these examples show clearly that the hydrogenation process can be carried out with other types of hydrogenation catalysts besides palladium-on-charcoal;.and

that catalytic hydrogenation of a nitro compound of the Formula (II) is not so unpredictable as the Examiner believes. Catalytic hydrogenation of nitro compounds to obtain amino compounds has been known to those "skilled in the art" for many years

and such a hydrogenation step is a common process used in organic synthesis. In such a process several types of hydrogenation catalysts can be used interchangeably so that one hydrogenation catalyst can be routinely substituted for another to obtain the same product with perhaps only some difference in product yield or purity. Therefore in principle it is highly predictable that the well-known and commonly used catalysts may be substituted for one another in hydrogenation of a nitro compound to form the corresponding amino compound. For instance one "skilled in the art" knowing that the use of Raney nickel to catalyze the hydrogenation of a nitro compound to form the amino compound would expect the hydrogenation to work if palladium were substituted as hydrogenation catalyst for the Raney nickel.

Accordingly no rejection of any claim should be maintained under 35 USC 112, first paragraph, for lack of an enabling disclosure.

The Examiner is Incorrect for Rejecting Claim 10 under 35 USC 112, Second Paragraph, on the Grounds that the Claims are Vague and Indefinite 37 CFR (C)(8)(ii)

The Examiner has raised a new issue in Paper No. 11 concerning the solvent which is stated in lines 10 and 11 as "an inert organic solvent" which the Examiner considers indefinite. The Examiner wants the Appellants to limit the definition of the inert organic solvent to the C1 to C4 alkanol of claim 13.

Appellants do not agree with the Examiner's basis for rejecting claim 10. There is no justification to limit the definition of the inert organic solvent to the C1 to C4 alkanol as Appellants would expect a large number of inert solvents to work as well for the catalytic hydrogenation of Claim 10, step (a). There is nothing indefinite about the term "an inert organic solvent" which is known in the art as a solvent that has little or no chemical action and will not interfere with the presently claimed synthesis. Appellants cite Hackh's Chemical Dictionary, Grant, p. 346, Fourth Edition (1968) which defines inert as "sluggish, having little or no chemical action." Perhaps such a definition is broad, but not indefinite. Decisions supporting Appellants' right to claim their hydrogenation catalyst broadly and their solvent broadly stating that such claims are neither vague and indefinite nor beyond the scope of the enabling disclosure include Ex parte Altermatt, 183 USPQ 436; Ex parte Laiderman175 USPQ 757; and In re Skoll, 187 USPQ 481.

CONCLUSION

For the reasons stated above Appellants conclude that the rejection of no claim on appeal as either beyond the scope of the enabling disclosure according to the first paragraph of 35 USC 112 or as indefinite according to the second paragraph of 35 USC 112 should be sustained. Appellants respectfully request the reversal of the rejection of all claims on these grounds.

This appeal brief is submitted in triplicate. The undersigned attorneys wish to charge the cost of filing this appeal brief to their credit card. The form authorizing the charge by credit card is enclosed.

Respectfully submitted,
The Firm of Karl F. Ross P.C.

By: Jonathan Myers, Reg. No. 26,963
Attorney for Applicant

Enc: Appeal Brief submitted in
Triplicate
PTO 2038 Charge Card Form
Copy of Hackh's Chemical Dictionary, Grant,
p. 346, Fourth Edition (1968)
(9) Appendix

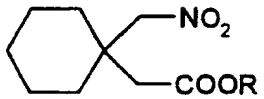
10 December 2003
5676 Riverdale Avenue Box 900
Bronx, NY 10471-0900
Cust. No.: 535
Tel: (718) 884-6600
Fax: (718) 601-1099

ge/

(9) Appendix

Claim 10 A process for preparing pure 1-(aminomethyl)-cyclohexyl-acetic acid or a pharmaceutically acceptable salt thereof which comprises the steps of

(a) catalytically hydrogenating a compound of the Formula (II)



(II)

wherein

R is hydrogen, benzyl or diphenylmethyl or aryl which is unsubstituted or substituted by a C_1 to C_4 alkyl or alkoxy group in the presence of a hydrogenation catalyst in an inert organic solvent at a temperature of 10 to 50°C under 1 to 20 kPa pressure to directly obtain the 1-(aminomethyl)-cyclohexyl-acetic acid in the inert organic solvent;

(b) filtering the 1-(aminomethyl)-cyclohexyl-acetic acid in the inert organic solvent prepared according to step (a) to remove the hydrogenation catalyst to obtain a filtrate;

c) concentrating the filtrate by removing a portion of the inert organic solvent to obtain pure 1-(aminomethyl)-cyclohexyl-acetic acid; and

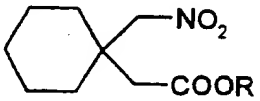
(d) in the case where a pharmaceutically acceptable salt is to be formed transforming the pure 1-(aminomethyl)-cyclohexyl-acetic acid into a pharmaceutically acceptable salt.

Claim 11 The process defined in claim 10 which further comprises the step of adding tetrahydrofuran to the concentrated filtrate obtained according to step c) to precipitate out pure 1-(aminomethyl)-cyclohexyl-acetic acid.

Claim 12 The process defined in claim 10 wherein according to step (a) the hydrogenation catalyst is palladium on activated carbon.

Claim 13 The process defined in claim 10 wherein according to step (a) the inert organic solvent is a C_1 to C_4 alcohol.

Claim 14 A compound of the Formula (II)



(II)

wherein
R is hydrogen, benzyl or diphenylmethyl or an aryl group which is unsubstituted or substituted by a C_1 to C_4 alkyl or alkoxy group.

Claim 15 1-(nitromethyl)cyclohexyl-acetic acid as defined in claim 14.

Claim 16 benzyl 1-(nitromethyl)-cyclohexyl-acetate as defined in claim 14.

Claim 17 diphenylmethyl 1-(nitromethyl)cyclohexyl-acetate as defined in claim 14.

Claim 18 The process defined in claim 10 wherein according to step (a) the hydrogenation catalyst is a rare metal, Raney nickel or cobalt.

21838

IN THE U.S. PATENT AND TRADEMARK OFFICE

Inventor	Tibor GIZUR et al
Patent App.	09/856,517 (US Nat'l phase of PCT/HU99/00102)
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Art Unit	1625 Examiner Oh, T

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Box 1450
Alexandria, VA 22313-1450

Appealed 15-Oct-03

APPEAL BRIEF UNDER 37 CFR 1.192(a)

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REAL PARTY IN INTEREST

The real party in interest is Richter Gedeon Vegyeszeti Gyar RT, Budapest, Hungary,

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There are no related appeals or interferences involving the instant application.

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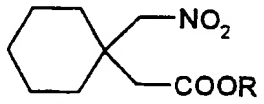
Appellants have discovered an invention with two particular features. One feature is a process for the preparation of pure (1-aminomethyl)-cyclohexyl acetic acid or a pharmaceutically acceptable salt thereof. This compound is an established pharmaceutically active ingredient known as gabapentin and is useful to

antagonize gamma-amino-butyric acid (GABA). See the original application on page 4, lines 27 and 28 through page 5, line 21 that shows the synthesis of the compound of the Formula (I) from the new compound of the Formula (II). Thus the compound of the Formula (I) or a pharmaceutically acceptable salt thereof is prepared by:

(a) catalytically hydrogenating a compound of the Formula (II)



(II)

wherein

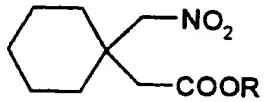
R is hydrogen, benzyl or diphenylmethyl or aryl which is unsubstituted or substituted by a C_1 to C_4 alkyl or alkoxy group in the presence of a hydrogenation catalyst in an inert organic solvent at a temperature of 10 to 50°C under 1 to 20 kPa pressure to directly obtain the 1-(aminomethyl)-cyclohexyl-acetic acid in the inert organic solvent;

(b) filtering the 1-(aminomethyl)-cyclohexyl-acetic acid in the inert organic solvent prepared according to step (a) to remove the hydrogenation catalyst to obtain a filtrate;

c) concentrating the filtrate by removing a portion of the inert organic solvent to obtain pure 1-(aminomethyl)-cyclohexyl-acetic acid; and

(d) in the case where a pharmaceutically acceptable salt is to be formed transforming the pure 1-(aminomethyl)-cyclohexyl-acetic acid into a pharmaceutically acceptable salt.
See also Example 1, part (b), appearing in the original application on page 6, lines 5 through 11 and Example 2 appearing in the original application on page 6, lines 13 through 21.

The second feature of the invention relates to the new structurally distinct compounds of the Formula (II)



(II)

wherein R is hydrogen, benzyl or diphenylmethyl or an aryl group which is unsubstituted or substituted by a C1 to C4 alkyl or alkoxy group. These new compounds of the Formula (II) are the starting materials in the present process used to prepare the desired pure (1-aminomethyl)-cyclohexyl acetic acid or a pharmaceutically acceptable salt thereof.

Appellants have found that where a new compound of the Formula (II) where R is hydrogen or R is benzyl, diphenylmethyl or aryl unsubstituted or substituted by alkyl or alkoxy, is hydrogenated in an inert organic solvent at a temperature of 10 to

50°C under 1 to 20 kPa pressure to directly obtain the desired 1-(aminomethyl)-cyclohexyl-acetic acid in an inert organic solvent, the product is obtained in high purity without formation of the spirolactam as shown in col. 5, line 40 of U.S. Patent 5,091,567 to GEIBEL et al. See page 4, lines 12 to 17 of the present application.

According to GEIBEL et al in col. 5, lines 30 to 40 when the starting compound in step 5) of the reference process is the ethyl ester instead of the free acid, or the benzyl, diphenylmethyl or aryl ester of the present Formula (II) the principal product obtained is the spirolactam which must then be treated with an acidic ion exchanger to eventually obtain the desired 1-(aminomethyl)-cyclohexyl-acetic acid. Only a small amount of the 1-(aminomethyl)-cyclohexyl-acetic acid is obtained by direct hydrogenation of the ethyl ester according to GEIBEL et al.

Both the new compound of the present Formula (II) where R is hydrogen (Formula IIa) or the new compound of the Formula (II) where R is benzyl, diphenylmethyl or aryl (Formula IIb) are key to successfully carrying out step (a) of claim 10 to obtain the desired 1-(aminomethyl)-cyclohexyl-acetic acid without the lactam formation. See page 1, lines 3 through 10 of the original application and original claims 6 through 9.

(6) THE ISSUES

The first issue is the scope of the hydrogenation catalyst in claim 10, step (a) which is directed to catalytically hydrogenating a compound of the Formula (II) in th presence of a

hydrogenation catalyst in an inert organic solvent at a temperature of 10 to 50°C under 1 to 20 kPa pressure to directly obtain the 1-(aminomethyl)-cyclohexyl-acetic acid in the inert organic solvent. The Examiner believes that the scope of the hydrogenation catalyst in claim 10 has not been enabled according to the requirements of 35 USC 112, first paragraph.

The second issue is whether Appellants' definition of the solvent used in the catalytic hydrogenation according to claim 10, step (a), as "an inert organic solvent" is indefinite for failure to particularly point out and distinctly claim the subject matter of the invention according to the requirements of 35 USC 112, second paragraph.

(7) GROUPING OF CLAIMS

Claim 10 is the only claim in the case that has been rejected under 35 USC 112, first paragraph, as beyond the scope of the enabling disclosure. Claim 10 is directed to a process for preparing a compound of the Formula (I) or a pharmaceutically acceptable salt thereof and the first step of the process involves the catalytic hydrogenation of the starting material of the Formula (II) with a hydrogenation catalyst. The Examiner has rejected claim 10 under 35 USC 112, first paragraph, on the grounds that the broad definition of the hydrogenation catalyst in step (a) is beyond the scope of the enabling disclosure. Claims 12 and 18 are dependent upon rejected base claim 10 and have been rejected solely because of the rejection of claim 10. Claims 12 and 18 have a more

limited definition of the hydrogenation catalyst than does claim 10, the Examiner has not specifically questioned the enablement of the hydrogenation catalysts defined in claim 12 and 18, and for this reason claims 12 and 18 do not stand or fall together with claim 10 on this issue. In fact the Examiner has indicated in Paper Number 11 at the top of page 3 that claims 11 through 18 have been rejected as being dependent on a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 13 is dependent upon claim 10 and limits the "inert organic solvent" called for in step (a) to a C1 to C4 alcohol. The Examiner has rejected claim 10 under 35 USC 112, second paragraph, as indefinite, on the grounds that "inert organic solvent" fails to particularly point out and distinctly claim what Appellants regard as their invention. The Examiner has not rejected claim 13 on this basis, however, since claim 13 limits the "inert organic solvent" to a C1 to C4 alcohol. Thus claim 13 does not stand or fall together with claim 10 on this issue.

Claims 14 through 17 are directed to new structurally distinct compounds of the Formula (II) which are the starting materials in the process of claim 10 for the preparation of the compound of the Formula (I) or a pharmaceutically acceptable salt thereof. Claims 14 through 17 are entirely independent of claim 10, are directed to a feature of the invention that is separate and distinct from the pure compound of the Formula (I) or pharmaceutically acceptable salt obtained according to the process of claim 10

and no basis for rejection of these claims has been set forth heretofore by the Examiner. It is noted that the scope of the definition of the hydrogenation catalyst in step (a) of claim 10 and the question of whether the term "inert organic solvent" is vague and indefinite have absolutely nothing to do with claims 14 through 17 directed to the new structurally distinct compounds of the Formula (II) where R is hydrogen, benzyl, diphenylmethyl or aryl unsubstituted or substituted by a C1 to C4 alkyl or alkoxy group.

For the reasons stated above, claim 10 does not stand or fall together with claims 12 and 13 through 18.

(8) THE ARGUMENTS

37 CFR 1.192 (c)(8)(i)(B)

The Examiner is Incorrect for Rejecting Claim 10 under 35 USC 112, first Paragraph, on the Grounds that the Claim is Supported by a Non-Enabling Disclosure

The Examiner has rejected the independent process of preparation claim 10 under 35 USC 112, first paragraph, on the grounds that the claim is not supported by an enabling disclosure. Specifically the Examiner is troubled by the broad term in line 10 "hydrogenation catalyst" which the Examiner considers to be too broad since the only hydrogenation catalyst that Appellants have successfully exemplified in the specification to hydrogenate a compound of the Formula (II) to form a compound of the Formula (III) is palladium on activated carbon. The Examiner is aware that

Appellants name other hydrogenation catalysts on page 4, lines 22 through 26 of the original specification. There Appellants mention "rare metal catalysts, e.g. rhodium or palladium, Raney nickel or cobalt catalysts.." The Examiner argues, however, that catalysis is an unpredictable art and the only hydrogenation catalyst that Applicants have shown to successfully hydrogenate a compound of the Formula (II) is palladium-on-carbon.

Appellants do not agree that catalytic hydrogenation is so unpredictable. Catalytic hydrogenation of nitro compounds to obtain amino compounds has been known to those "skilled in the art" for many years and such a hydrogenation step is a common process used in organic synthesis. In such a process several types of hydrogenation catalysts can be used interchangeably so that one hydrogenation catalyst can be routinely substituted for another to obtain the same product with perhaps only some difference in product yield or purity. Therefore in principle it is highly predictable that the well-known and commonly used catalysts may be substituted for one another in hydrogenation of a nitro compound to form the corresponding amino compound. One "skilled in the art" knowing that the use of Raney nickel to catalyze the hydrogenation of a nitro compound to form the amino compound would also work if palladium were substituted as hydrogenation catalyst for the Raney nickel.

Appellants note that claim 1 of U.S. Patent 5,091,567 to GEIBEL et al defines the hydrogenation catalyst as "a noble metal catalyst" even though the only noble catalyst that is exemplified

(see Examples 8 and 15) or even named (see col. 5, lines 46 and 47) in the reference is palladium-on-carbon.

The Examiner has made an argument that case law written by the U.S. Patent and Trademark Office Board of Appeals and by the Courts supports the Examiner's argument that the definition of the hydrogenation catalyst should be limited because catalysis is an unpredictable art and more than routine experimentation would be needed to determine which hydrogenation catalysts known in the art would actually work to reduce the present Formula (II) compound to form the Formula (I) compound and which would not work. The Examiner has cited In re Wands, 8 USPQ 2d 1400 (CAFC 1988) and Ex parte Forman, et al, 230 USPQ 546 (PTO Bd. App. 1986) when he mentions "Forman factors or Wands factors" on page 2 of Paper No. 7. Appellants do not believe that either of these decisions is relevant to the present case. In Forman the Examiner did raise the issues of enablement and undue experimentation under 35 USC 112, first paragraph, just as in the present case, but the facts are so far removed from the present case, that the decision is not applicable. The Forman decision does not relate to catalytic hydrogenation, but relates to a new vaccine for immunizing a patient against enteric diseases. with a genetic hybrid bacterium as the active ingredient. In Forman the questions of enablement and undue experimentation relate to how the active ingredient in the vaccine is prepared. The Examiner argued that one of the starting materials, a particular S. typhi mutant strain was not commercially available and in the absence of a permanent deposit by the appli-

cant, one "skilled in the art" could not make the active ingredient for the vaccine without the need to carry out undue experimentation. The Examiner also argued that the process used to prepare the active ingredient in Forman, known as hyperconjugation, is a new process and it is unpredictable as to the results that will be obtained. The fact that the Patent and Trademark Office Board of Appeals agreed with the examiner in Forman that the application did not contain a sufficient disclosure to enable the practice of the invention in no way provides any basis for the Examiner's rejection of the claims in the present application for lack of enablement. While there may be some unpredictability associated with catalysis, catalytic hydrogenation is an old, well-known process unlike hyperconjugation and so Forman should not apply. The broad definition of the hydrogenation catalyst as a noble metal found in the independent claim of U.S. Patent 5,091,567 supports Appellants' argument that catalytic hydrogenation is not the equivalent of hyperconjugation in terms of predictability.

The Wands decision is also a decision in the biotech field that does not relate to catalytic hydrogenation. The Wands decision relates to an immunoassay method for the hepatitis B surface antigen (HbsAg) using high affinity monoclonal antibodies of the IgM isotype and that these particular monoclonal antibodies detected the antigen with surprisingly high sensitivity and specificity. The Examiner argued that the specification in Wands was not enabling because (1) there was no deposit in a permanent depository of the hybridomas needed to secrete the monoclonal

antibodies and (2) there was not enough disclosure of how to produce the high affinity monoclonal antibodies of the IgM isotype without the need to conduct undue experimentation since the data in the Wands application showed that the process to produce such monoclonal antibodies was unpredictable and unreliable and would require undue experimentation of one "skilled in the art" trying to practice the Wands invention. Specifically only a fraction of the hybridomas produced by Wands in the fusion process produced monoclonal antibodies that were effective in binding to the HbsAg. Thus the examiner and the Board of Appeals considered the Wands process to be too unpredictable and required an undue amount of experimentation to successfully practice the invention. Furthermore the examiner and the Board of Appeals concluded that in the absence of a deposit of the viable hybridomas in a permanent depository, the enablement requirement of the patent statute was not satisfied.

The Court ruled that none of the arguments by the Examiner or the Board was sustainable and reversed the rejection of the claims as based upon an inadequate disclosure. The Court made it clear that there is no requirement of depositing the hybridomas in a permanent depository when the specification itself would enable one "skilled in the art" to prepare without the need to conduct undue experimentation hybridomas that will secrete the monoclonal antibodies. Furthermore the fact that one would have to screen hybridomas to find out which ones produce viable monoclonals does not amount to "undue experimentation" even if the majority of

the hybridomas do not produce the viable monoclonals. Such experimentation would be expected. Thus the Court ruled in favor of the applicant and against the Patent and Trademark Office. Thus the Wands decision in no way supports the Examiner's argument that the present application is not enabling to support the catalytic hydrogenation as presently claimed.

In fact Wands is actually supportive of the Applicants' position since Wands makes it clear that a certain amount of experimentation is entirely acceptable in practicing the invention disclosed in a U.S. Patent. In the present case one "skilled in the art" could pick and choose among conventional hydrogenation catalysts such as a platinum group metal or Raney nickel and determine which ones catalyze the hydrogenation of the Formula (II) compound the best.

The Examiner has also cited Ex parte Sizto, 9 USPQ 2d 2081 (Bd. App. 1988) to provide support for his argument that catalysis is an unpredictable art. In Sizto an analytical method is claimed using a catalyst which facilitates a reaction between an analyte (unknown) and a solute (reagent). Such a reaction permits the determination of the presence or absence of the analyte in a given sample. The process claims a "catalyst" without any further qualification whatsoever even though the only catalyst actually exemplified in but one example is an enzyme. The examiner and the Board of Appeals both agreed that the term catalyst was too broad because there was no limitation whatsoever on the identity or the function of the catalyst. The Board specifically pointed out that

there are many catalysts that are not enzymes and there is no evidence that any catalyst that is not an enzyme will work in the Sizto method. Other catalysts that were originally contemplated by Sizto included metal complexes and electron transfer agents which are far removed from enzymes. Furthermore the Board noted that one of the other reagents in the analytical method had to be an enzyme even where the applicant planned to use a non-enzyme catalyst. The Board indicated that it was highly speculative that such a method would work where the catalyst was anything but an enzyme and affirmed the rejection.

The present process is directed to the catalytic hydrogenation of a nitro compound of the Formula (II) using a hydrogenation catalyst. Hydrogenation catalysts are typically metals and do not encompass enzymes or the other diverse kinds of catalysts mentioned in Sizto. The holding in Sizto is not that catalysis in general is unpredictable, but that the kind of catalysis called for by the analytical method of Sizto is unpredictable if catalysts other than enzymes are contemplated. Thus Sizto provides no basis for the Examiner's requirement that Appellants limit the catalyst in their hydrogenation process to palladium-on-carbon.

The Examiner has also cited In re Armbruster, 185 USPQ 152 (CCPA 1975) which is directed to a process for hydrolyzing starch to obtain a starch product having a dextrose equivalent (D.E.) less than 15 using bacterial alpha-amylase to increase the D.E. The application also disclosed that the process was useful to obtain a starch hydrolysate with a D.E. of 5 to 15. The examiner

took the range of 5 to 15 to mean that a starch hydrolysate with a D.E. less than 5 would not be operative. The issue here was not the scope of the kinds of enzymes used to facilitate the hydrolysis, but whether the applicant really established that his process could obtain the starch hydrolysate product having a D.E. less than 15, including a D.E. below 5 is still a useful product. The Court held that the examiner had insufficient evidence to establish that a starch hydrolysate with a D.E. less than 5 would be inoperative and only made such a speculation based upon the lower end of this disclosed range.

There is no similarity whatsoever between the facts in Armbruster and those in the present case since the process in the present case includes no range where one portion of that range arguably could encompass inoperative subject matter. Furthermore the Court in Armbruster ruled in favor of the appellant and against the Patent and Trademark Office on the issue of enablement and so the decision actually helps the present Appellants more than it helps the Examiner's position. Nothing in the Armbruster decision supports any argument that the claims in the present case with the broadly defined hydrogenation catalyst cover catalysts that will not work and the decision leaves it to the Examiner to prove that any such catalyst within the scope of the presently claimed invention will not work.

Finally In re Angstadt and Griffin, 190 USPQ 1976 (CCPA 1976) has been cited for its disclosure that catalytic processes are unpredictable and that the scope of the enablement varies

inversely with the degree of unpredictability. The examiner and the Board of Appeals questioned whether the claimed process which was a process to catalytically oxidize secondary or tertiary alkyl aromatic hydrocarbons to form a reaction mixture containing the corresponding hydroperoxide using an organometallic complex as the catalyst. The application also stated that some of the catalyst complexes will not effectively facilitate oxidation of the starting materials. The Court reversed the examiner and the Board stating that the evidence as a whole showed that the process was operative notwithstanding that some particular catalysts may be inoperative. The Court held essentially that some experimentation by one "skilled in the art" seeking to work the patent to find the best catalysts for the process does not amount to "undue experimentation" and is permissible under the patent statute. Thus this decision is supportive of the right of the present Appellants to obtain a patent with the broad definition of the hydrogenation catalyst.

Furthermore Appellants have carried out additional examples showing catalytic hydrogenation of the compound of the Formula (II) where R is hydrogen to yield 1-(aminomethyl)cyclohexyl acetic acid of the Formula (I). Instead of palladium, the catalysts tested were Raney nickel and Adams catalyst. The examples are as follows:

Example 3

1-(nitromethyl)cyclohexane acetic acid (6.27 g; 0.031 mol) was dissolved in methanol (75 ml). To the solution Raney Ni catalyst (1 g) was added and was hydrogenated at atmospheric

pressure. The catalyst was filtered off and the filtrate was evaporated in vacuo. To a residue was added tetrahydrofuran (60 ml). The crystalline product was filtered off and dried.

Yield: 2.1 g (39.6 %)

Melting point: 165-9°C

Example 4

1-(nitromethyl)cyclohexane acetic acid (6.27 g; 0.031 mol) was dissolved in methanol (75 ml). To a solution Adams catalyst (0.07 g) was added and was hydrogenated at atmospheric pressure. The catalyst was filtered off and the filtrate was evaporated in vacuo. To the residue was added tetrahydrofuran (60 ml). The crystalline product was filtered off and dried.

The examples show clearly that the hydrogenation process can be carried out with other types of catalysts.

Appellants have made these additional examples of record on 16 May 2003 in a Declaration Under 37 CFR 1.132 signed by Dr. Tibor Gizur, one of the Appellants. In the declaration, Dr. Gizur concluded as follows:

that these examples show clearly that the hydrogenation process can be carried out with other types of hydrogenation catalysts besides palladium-on-charcoal;.and

that catalytic hydrogenation of a nitro compound of the Formula (II) is not so unpredictable as the Examiner believes. Catalytic hydrogenation of nitro compounds to obtain amino compounds has been known to those "skilled in the art" for many years

and such a hydrogenation step is a common process used in organic synthesis. In such a process several types of hydrogenation catalysts can be used interchangeably so that one hydrogenation catalyst can be routinely substituted for another to obtain the same product with perhaps only some difference in product yield or purity. Therefore in principle it is highly predictable that the well-known and commonly used catalysts may be substituted for one another in hydrogenation of a nitro compound to form the corresponding amino compound. For instance one "skilled in the art" knowing that the use of Raney nickel to catalyze the hydrogenation of a nitro compound to form the amino compound would expect the hydrogenation to work if palladium were substituted as hydrogenation catalyst for the Raney nickel.

Accordingly no rejection of any claim should be maintained under 35 USC 112, first paragraph, for lack of an enabling disclosure.

The Examiner is Incorrect for Rejecting Claim 10 under 35 USC 112, Second Paragraph, on the Grounds that the Claims are Vague and Indefinite 37 CFR (C)(8)(ii)

The Examiner has raised a new issue in Paper No. 11 concerning the solvent which is stated in lines 10 and 11 as "an inert organic solvent" which the Examiner considers indefinite. The Examiner wants the Appellants to limit the definition of the inert organic solvent to the C1 to C4 alkanol of claim 13.

Appellants do not agree with the Examiner's basis for rejecting claim 10. There is no justification to limit the definition of the inert organic solvent to the C1 to C4 alkanol as Appellants would expect a large number of inert solvents to work as well for the catalytic hydrogenation of Claim 10, step (a). There is nothing indefinite about the term "an inert organic solvent" which is known in the art as a solvent that has little or no chemical action and will not interfere with the presently claimed synthesis. Appellants cite Hackh's Chemical Dictionary, Grant, p. 346, Fourth Edition (1968) which defines inert as "sluggish, having little or no chemical action." Perhaps such a definition is broad, but not indefinite. Decisions supporting Appellants' right to claim their hydrogenation catalyst broadly and their solvent broadly stating that such claims are neither vague and indefinite nor beyond the scope of the enabling disclosure include Ex parte Altermatt, 183 USPQ 436; Ex parte Laiderman175 USPQ 757; and In re Skoll, 187 USPQ 481.

CONCLUSION

For the reasons stated above Appellants conclude that the rejection of no claim on appeal as either beyond the scope of the enabling disclosure according to the first paragraph of 35 USC 112 or as indefinite according to the second paragraph of 35 USC 112 should be sustained. Appellants respectfully request the reversal of the rejection of all claims on these grounds.

This appeal brief is submitted in triplicate. The undersigned attorneys wish to charge the cost of filing this appeal brief to their credit card. The form authorizing the charge by credit card is enclosed.

Respectfully submitted,
The Firm of Karl F. Ross P.C.

By: Jonathan Myers, Reg. No. 26,963
Attorney for Applicant

Enc: Appeal Brief submitted in Triplicate
PTO 2038 Charge Card Form
Copy of Hackh's Chemical Dictionary, Grant, p. 346, Fourth Edition (1968)
(9) Appendix

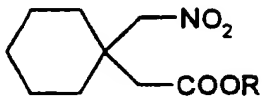
10 December 2003
5676 Riverdale Avenue Box 900
Bronx, NY 10471-0900
Cust. No.: 535
Tel: (718) 884-6600
Fax: (718) 601-1099

ge/

(9) Appendix

Claim 10 A process for preparing pure 1-(aminomethyl)-cyclohexyl-acetic acid or a pharmaceutically acceptable salt thereof which comprises the steps of

(a) catalytically hydrogenating a compound of the Formula (II)



(II)

wherein

R is hydrogen, benzyl or diphenylmethyl or aryl which is unsubstituted or substituted by a C_1 to C_4 alkyl or alkoxy group in the presence of a hydrogenation catalyst in an inert organic solvent at a temperature of 10 to 50°C under 1 to 20 kPa pressure to directly obtain the 1-(aminomethyl)-cyclohexyl-acetic acid in the inert organic solvent;

(b) filtering the 1-(aminomethyl)-cyclohexyl-acetic acid in the inert organic solvent prepared according to step (a) to remove the hydrogenation catalyst to obtain a filtrate;

c) concentrating the filtrate by removing a portion of the inert organic solvent to obtain pure 1-(aminomethyl)-cyclohexyl-acetic acid; and

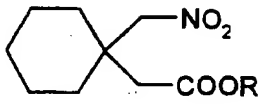
(d) in the case where a pharmaceutically acceptable salt is to be formed transforming the pure 1-(aminomethyl)-cyclohexyl-acetic acid into a pharmaceutically acceptable salt.

Claim 11 The process defined in claim 10 which further comprises the step of adding tetrahydrofuran to the concentrated filtrate obtained according to step c) to precipitate out pure 1-(aminomethyl)-cyclohexyl-acetic acid.

Claim 12 The process defined in claim 10 wherein according to step (a) the hydrogenation catalyst is palladium on activated carbon.

Claim 13 The process defined in claim 10 wherein according to step (a) the inert organic solvent is a C_1 to C_4 alcohol.

Claim 14 A compound of the Formula (II)



(II)

wherein
R is hydrogen, benzyl or diphenylmethyl or an aryl group which is unsubstituted or substituted by a C_1 to C_4 alkyl or alkoxy group.

Claim 15 1-(nitromethyl)cyclohexyl-acetic acid as defined in claim 14.

Claim 16 benzyl 1-(nitromethyl)-cyclohexyl-acetate as defined in claim 14.

Claim 17 diphenylmethyl 1-(nitromethyl)cyclohexyl-acetate as defined in claim 14.

Claim 18 The process defined in claim 10 wherein according to step (a) the hydrogenation catalyst is a rare metal, Raney nickel or cobalt.

HACKH'S
CHEMICAL DICTIONARY

[*American and British Usage*]

Containing the Words Generally Used in Chemistry, and Many of the Terms Used in the Related Sciences of Physics, Astrophysics, Mineralogy, Pharmacy, Agriculture, Biology, Medicine, Engineering, etc.

Based on Recent Chemical Literature

FOURTH EDITION

Completely Revised and Edited by

JULIUS GRANT

M.SC., PH.D., F.R.I.C. CHEMICAL CONSULTANT

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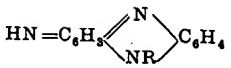
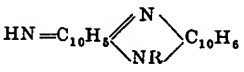
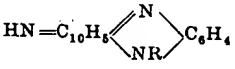
indulines. Blue or black dyestuffs, from the tricyclic ring



Substitution is usually at the N atom indicated. **benz-** Aposafranine. **naphth-** Dyestuffs of the type



ros- Dyestuffs of the type



indurated. Hardened, as in the firing of clays.
indyl. The radical C_8H_6N—, from indole. **iso-** See *isoindyl.*
-ine. Suffix indicating: (1) a halogen, as chlorine; (2) a hydrocarbon of the acetylene series, as butine; (3) an alkaloid or nitrogen base, as morphine. Cf. *-in.*
inert. Sluggish; having little or no chemical action. **i. elements.** The noble gases of the "zero" group of the periodic system which have no valency and do not combine with other elements. **i. substance.** A substance that is resistant to chemical or physical action.
inertia. The tendency of a physical body to remain in an unchanged condition, either in a state of uniform motion, or at rest. **moment of i.** A factor in the mathematic treatment of the rotation of a body in terms of mass and squares of the linear dimensions. Cf. *momentum.*
infection. Transmission of disease by contact, due to the successful invasion and growth of bacteria or parasites in the tissues of an organism. Cf. *contamination.* **aerial-** I. caused by dust particles in air. **focal-** I. in which the bacterial growth is restricted to a small area of the organism. **mixed-** I. caused by more than one kind of bacterium.
infectious disease. A pathological condition produced by invasion and growth by microorganisms (bacteria or protozoa).
infiltration. (1) The deposition of minerals from solution in the pores of a rock. (2) The slow diffusion of injected solutions into the tissues of an organism.
infinitesimal. Smaller than any assigned quantity. Negligible.
inflammable. Flammable. **i. air.** The original name for hydrogen.
infra. Beyond. **i. luminescence.** Luminescence whose wavelengths are in the infrared region. **i. phonic.** Vibrations in air of wavelength too high to be audible. **i. photic.** Radiations of a wavelength too long to be visible; as, i. red. **i. red.** Ultrared. The invisible part of the spectrum from 10^{-4} to 10^{-1} cm, which overlaps a portion of the visible spectrum. Cf. *radiations-long-* I.r. rays from 14,000 to 150,000 Å. *near-* or *short-* I.r. rays from 7,200 to 14,000 Å. Sources: see table. **i. röntgen rays.** Grenz rays. **i. sonic.** I. phonic.

	Infrared rays, %	Visible rays, %
Sunlight	60	34
Incandescent lamp	95	4.8
Carbon arc	80	15
Resistance wire	99	0.5

infundibuliform. A funnel-shaped bacterial growth.
infusible. Not capable of being fused. **i. white precipitate.** Mercuridiammonium chloride.
infusion. Infusum. A solution obtained by steeping vegetable drugs in water below its boiling point, and straining. Cf. *decoction.*
infusoria. A class of protozoa. Erroneously applied to diatoms (protophyta).
infusorial earth. Diatomaceous earth, tripolite, kieselguhr. A light, earthy, sedimentary rock consisting of empty shells of diatoms and other protophyta. Used as a filtration aid, and adsorbent.
infusum. Infusion.
ingluvin. An enzyme from hen gizzards used to treat dyspepsia.
ingredient. Any constituent of a mixture. Cf. *constituent.*
inhaler. (1) A device to administer vapors or gases. (2) A device to filter dust from air to be breathed. Cf. *respirator.*
inhibin. The testicular hormone that prevents overdevelopment of the pituitary gland.
inhibition. A restraint or encumbrance.
inhibitor. A substance that arrests a chemical action. **vapor-phase-** An organic compound which is solid at ordinary temperatures, and which evolves a vapor which surrounds a metal article in a closed container and produces on its surface an invisible protective film; e.g., nitrites of nitrogen bases. Cf. *vapor.*
inhibitory phase. Protective *colloid.*
initiator. Trigger. Cf. *promoter.*
-inium. -ium. **i. compound.** Compounds of organic nitrogen bases with acids in which N is assumed to be pentavalent; as, pyridinium. Cf. *-ilium.*
injection. The administration of a substance into a part of an organism: intravenously (into the bloodstream), intramuscularly (into muscular tissue), or subcutaneously (under the skin). **i. needle.** A hypodermic needle. **i. syringe.** A graduated glass tube, with piston, used to inject liquid into an organism.
ink. (1) A colored liquid, used for writing. (2) A colored paste or liquid used for printing. **aniline-** A solution of an aniline dye in a volatile solvent or dilute gum; used for printing in bright colors or at high speeds, e.g., by the gravure process. **canceling-** A suspension of lampblack in oil, used for stamp pads. **Chinese-** India i. **copying-** An iron-tannic acid i. **diamond-** A mixture of barium sulfate and hydrofluoric acid, used for writing on glass. **flexographic-** Aniline i. **fugitive-** An i. that disappears on treatment with water or bleaching chemicals. Used for printing checks. **india-** Finely divided lampblack suspended in water or gum. **invisible-** Secret i., sympathetic